Acute Lymphoblastic Leukemia Atypically Presenting with Severe Hypercalcemia in a Palestinian Child

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BACKROUND

Malignancy-associated hypercalcemia(MAH) is rare in the pediatric population with incidence varying between0.6 and 4.8% in comparison to adult patients • (10 - 40%) (1). It is commonly associated with solid tumor malignancies, but less often with hematologic malignancies. However, this complication usually presents as a late finding in pediatric patients and may lead to life-threatening effects on neuromuscular, renal ,gastrointestinal, skeletal, and cardiovascular systems, therefore, urgent intervention aims to minimize calcium serum concentration with enhancing physiological calcium excretion and to prevent its further end organs sequences using aggressive intravenous hydration, loop diuretics, bisphosphonate and calcitonin in addition to the treatment of the underlying cause.Here we present a case of Palestinian 10-year-female child who presented with gastrointestinal symptoms and severe hypercalcemia and diagnosed to have a pre-B acute lymphoblastic leukemia (ALL) even before the appearance of circulating blasts in the peripheral blood smear.

CASE PRESENTATION

Present illness of a 10 year old female otherwise healthy began 10 days prior to admission with generalized fatigue and decreased appetite, associated with polydipsia and recurrent vomiting. After that, she started to have localized not radiating epigastric abdominal pain with low grade fever.

Physical examination showed features of moderate dehydration and pallor. Her axillary temperature was 38.8 ºC, pulse rate was 146/min, blood pressure 121/54 mmHg, respiratory rate 28/min, weight 33 kg (90th percentile) and height 136 cm (60th percentile).

Laboratory investigations showed severe hypercalcemia (serum calcium 17.8mg/dl) with anemia and thrombocytopenia (Table 1). The patient was hospitalized in pediatric intensive care unit for further evaluation and management.

Thyroid and liver function tests , albumin, magnesium, lipid and coagulation profile and arterial blood gas analysis were found to be normal. Serum levels of PTH and 1,25-$(OH)_2$ Vitamin D were below normal. Serum cortisol, prolactin, were normal. Chest x ray, ECG and echocardiography were normal. Abdominal and thyroid ultrasound were normal. Peripheral blood smear revealed normochromic normocytic erythrocytopenia, leukopenia and thrombocytopenia without blasts.

Initially, Aggressive hydration by one and half times of the maintenance normal saline was started and furosemide 1 mg/kg IV every 12 hours in addition to bisphosphonate 1mg/kg IV infusion over 6 hourswere started. Allopurinol 10mg/kg in two divided doses daily was started for hyperuricemia. The patient was also started on ceftriaxone and vancomycin after blood and urine culture were taken. Serum calcium levels decreased gradually during the next few days of hospitalization and normalized at 4th day with 8.7 mg/dl level. None of the features in the child's history, physical, biological, or imaging work-up were suggestive of a specific cause, so bone marrow biopsy and aspirate were considered at 5th day of hospitalization which was consistent with pre B acute lymphoblastic leukemia (75% blast cells, lymphocytes 6.5%) in spite of absence of circulating blasts in the peripheral blood smear. Bone marrow flowcytomery was performed and was positive for CD34(38%), CD20(32%), CD10(98%), CD19(25%), HLADR(90%), cytoplasmic TDT(89%) and cytoplasmic CD79a(88%). The patient underwent ALL IC-BFM 2002chemotherapy protocol.

PARAMETER	VALUE	UNITS	NORMS	REMARKS
Hemoglobin	9.8	g/dL	12-16	
White Blood Cells	4100	cell/µl	4500-1000	neutrophils 38%, lymphocytes 61%, monocytes 1%
Platelets	32x10^9	cell /µL	150-450 x10^9	
Serum calcium	17.8	mg/dl	8.8-10.8	
Serum phosphor	3.6	mg/dl	1.5-6.8	
Parathyroid hormone	7.1	pg/ml	10-65	
Alkaline phosphatase	93	U/L	35-105	
1,25$(OH)_2$D	1.5	pg/ml	20-70	
Uric acid	10.8	m/dl	2.4-5.7	
LDH	357	U/L	207-414	

Table 1. Summary of laboratory results.

DISCUSSION

We describe a case of pediatric acute lymphoblastic leukemia (ALL) who presented with severe hypercalcemia and absence of blasts in the peripheral blood film. Hypercalcemia as an early presenting manifestation in childhood leukemic patients is rare and usually presents as a late complication. The underlying mechanism of hypercalcemia in ALL has not been established well. Malignant hypercalcemia in approximately 80% of reported cases is caused by parathyroid hormone-related protein (PTHrP) secreted from the tumor cells which binds to the same receptors as PTH through the production of various cytokines, such as interleukin-1 and -6, and tumor necrosis factor (TNF)-α and beta. Thus increasing bone resorption by activating osteoclast cells and therefore increasing calcium reabsorption from the distal tubule. The second mechanism is direct invasion of the skeleton by tumor cells with activating osteoclasts which are formed by the breakdown of bone.

Bisphosphonates use is limited in patients with compromised renal function, due to drug induced nephrotoxicity. In our patient, calcium level normalized after 4 days of aggressive hydration and bisphosphonate treatment. Calcitonin as adjunctive initial therapy can be used to inhibit calcium and phosphorus resorption from bone and increases the renal calcium excretion.

The prognosis of childhood ALL presenting by hypercalcemia is apparently not poor; however, this has not been established and needs to be verified in large prospective studies.

CONCLUSIONS

Case of a Palestinian child who presentedwith severe hypercalcemia as the initial manifestation ofpre-B acute lymphoblastic leukemia (ALL) and before even the appearance of circulating blasts in the peripheral blood smear.We emphasize thatmalignancy should be kept in mindas a differential diagnosis of childhood hypercalcemia with undetermined etiology.

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Bone, growth plate and mineral metabolism

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